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(54) Title: QUATERNARY SALTS OF 2-HYDROXY ACIDS

(57) Abstract

Quaternary salts of 2-hydroxy acids with an alkanolamine such as monoethanolamine, diethanolamine or triethanolamine are useful for incorporation in skin and cosmetic formulations. The acid may contain 2 to 24 carbon atoms, preferably 2 to 17 carbon atoms. The monoethanolamine, diethanolamine and triethanolamine salts of 2-hydroxy acids such as glycolic, lactic, 2-hydroxydecanoic, 2-hydroxyoctanoic and 2-hydroxylauric acid are quite water-soluble and cosmetic formulations containing such salts are non-irritating to the skin.

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QUATERNARY SALTS OF 2-HYDROXY ACIDS

Background of the Invention

Alpha-hydroxy acids (i.e. 2-hydroxy acids) are known in the prior art. Such acids are used extensively in cosmetic formulations. However, there are a number of disadvantages associated with the use of such acids in cosmetic formulations. In particular, such acids are generally insoluble in water or other non-toxic solvents. Moreover, these acids can be highly corrosive effect to the skin.

Objects of the Invention

It is an object of the invention to provide 2-hydroxy acid compositions which will be highly soluble in water and other non-toxic solvents commonly used in cosmetic formulations (e.g. 1,3-butylene glycol).

It is a further object of the invention to provide 2-hydroxy acid compositions which will be less irritating to the skin than prior art 2-hydroxy acids when incorporated into cosmetic formulations.

Details of the Invention

The objects of the invention have been met by providing novel quaternary salts of 2-hydroxy acids. Such salts will be the quaternary salts of the 2-hydroxy acids with an alkanolamine which may be monoethanolamine, diethanolamine or triethanolamine.

The quaternary salts of the 2-hydroxy acids will have a formula selected from the group consisting of:

$$R\text{-}CH(OH)\text{-}COO^{-}\ \overset{+}{N}H_3CH_2CH_2OH$$

$$R\text{-}CH(OH)\text{-}COO^{-}\ \overset{+}{N}H_2(CH_2CH_2OH)_2 \quad \text{and}$$

$$R\text{-}CH(OH)\text{-}COO^{-}\ \overset{+}{N}H(CH_2CH_2OH)_3$$

wherein R is hydrogen or a C_1-C_{22}, preferably C_3-C_{15}, alkyl group.

The 2-hydroxy acid will generally be one which has 2 to about 24, preferably 2 to 17, carbon atoms. Preferable examples of such 2-hydroxy acids include glycolic acid, lactic acid, 2-hydroxydecanoic acid, 2-hydroxyoctanoic acid and 2-hydroxylauric acid.

The 2-hydroxy acid quaternary salts of the invention may be readily prepared as follows:

(a) dissolve the selected 2-hydroxy acid in a non-reactive solvent;

(b) add an alkanolamine selected from the group consisting of monoethanolamine, diethanolamine and triethanolamine to the solution resulting from step (a); and

(c) recover the quaternary salt from the reaction mixture resulting from step (b) or utilize the quaternary salt in the form of a solution without recovery thereof.

In step (a), the choice of solvent is not critical so long as it is one which is non-reactive with the selected 2-hydroxy acid or the selected alkanolamine. Thus the solvent may be non-polar in nature such as methylene chloride, ethyl acetate, n-hexane, n-heptane and the like; alternatively, the solvent may be polar in nature such as water or a non-toxic solvent such as isopropanol, 1,3-butylene glycol, isocetyl alcohol, etc. Preferably, the non-reactive solvent is non-polar in nature such as methylene chloride. Typically, 15 to 30 parts by weight of the selected 2-hydroxy acid will be utilized per 100 parts by weight of the selected non-polar solvent. Step (a) is conveniently carried out at temperatures of about 15 to 50°C.

In step (b), the selected alkanolamine is added, with stirring, to the solution of the 2-hydroxy acid. Generally, the alkanolamine will be utilized in an amount corresponding to the stoichiometric amount required for the selected 2-hydroxy acid. Step (b) is also conveniently carried out at temperatures of about 15 to 50°C. The reaction between the 2-hydroxy acid and the alkanolamine proceeds fairly

quickly and is exothermic in nature. Therefore, cooling the reaction mixture to a temperature of about 25 to 35°C and adding the alkanolamine slowly, e.g. over a period of time of about 0.5 to 1 hour, is desirable.

In step (c), the quaternary salt will precipitate out if the selected solvent was non-polar in nature and is readily recovered by filtration. Typically, the salt will be washed with non-polar solvents such as methylene chloride and/or n-heptane to remove any unreacted components and thereafter dried (in air and/or vacuum-dried at temperatures of about 40 to 70°C). Alternatively, if the selected solvent was a non-toxic polar solvent and it is desired to manufacture a solvent solution of the quaternary salt, the salt need not be recovered from the reaction mixture.

Typically, the yield of the quaternary salt will be nearly quantitative, e.g. 80-98% of theory. The quaternary salts of the 2-hydroxy acids of the invention will typically have a water solubility of about 15 to 30 wt.%.

The following examples shall serve to illustrate the invention. Unless otherwise indicated, all parts and percentages are on a weight basis.

Example 1

A 3-liter, 3-neck flask was equipped with a stirrer, thermometer, condenser, addition funnel and a heating/cooling bath. 282 g (1.5 m) of 2-hydroxydecanoic acid were placed in the flask together with 1.5 kg of methylene chloride. Stirring was commenced and the temperature was adjusted to 30°C. 223.8 g (1.5 m) of triethanolamine was added, while stirring the reaction mixture, over a period of 1 hour, while the temperature of the reaction mixture was maintained in the range of 27 to 33°C by external cooling.

The reaction mixture was stirred for an additional two hours, while maintaining the temperature at 35°C. The reaction

mixture was then cooled to 20°C and the precipitate was collected by filtration. The product (i.e. the precipitate) was washed with 500 g methylene chloride and thereafter washed with 300 g of n-heptane. The product was air-dried for several hours and thereafter dried under vacuum at 50-60°C for 4 hours. The product yield was 481 g (95% of theory). The product was soluble in water in excess of 20 wt.%.

Example 2

Example 1 was repeated using 188 g (1.0 m) of 2-hydroxy-decanoic acid, 940 g methylene chloride and 105 g (1.0 m) of diethanolamine. After working up the product in the same manner, 273 g of product (93.2% of theory) was obtained. The product was soluble in water in excess of 20 wt.%.

Example 3

Example 1 was repeated using 160 g (1.0 m) 2-hydroxyoctanoic acid, 1.0 kg methylene chloride and 149.2 g (1.0 m) of triethanolamine. After working up the product in the same manner, 290 g of product (94% of theory) was obtained. The product was soluble in water in excess of 20 wt.%.

Example 4

Example 3 was repeated using 105 g (1.0 m) of diethanolamine instead of the triethanolamine. 236 g (89% of theory) of product was obtained. The product was soluble in water in excess of 20 wt.%.

Example 5

Example 1 was repeated using a 1-liter, 3-neck flask. 25.33 g (0.33 m) of glycolic acid was dissolved in 200 ml ethyl acetate at a temperature of 35-45°C. Thereafter, 49.7 g (0.33 m) of triethanolamine was added over a period of one hour and stirring was continued for 2 hours at 40°C. 69 g (92% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

Example 6

Example 1 was repeated using 212 g (1.0 m) of 2-hydroxylauric acid, 1.5 kg methylene chloride and 149.2 g (1.0 m) triethanolamine). 346 g (95.8% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

Example 7

Example 6 was repeated using 105 g (1.0 m) of diethanolamine instead of the triethanolamine. 346 g (95.8% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

Example 8

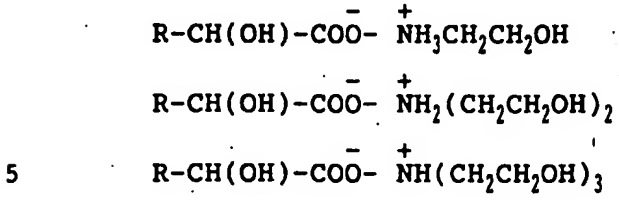
Example 1 was repeated using a 1-liter, 3-neck flask. 29.5 g of 85% d-l lactic acid (0.28 m) was dissolved in 150 g of isopropanol at a temperature of 35-45°C. Thereafter, 41.7 g (0.28 m) of triethanolamine was added over a period of one hour and stirring was continued for 2 hours at 35°C. The reaction mixture was cooled to 5°C and the product was filtered and washed with isopropanol and thereafter vacuum-dried. 56 g (84% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

Example 9

Example 3 was repeated using 100 g (0.625 m) 2-hydroxy-octanoic acid, 550 g methylene chloride and 38.2 g (0.625 m) of monoethanolamine. After working up the product in the same manner, 121 g of product (87.6% of theory) was obtained. The product was soluble in water in excess of 20 wt.%.

WHAT IS CLAIMED IS:

1. A quaternary salt of a 2-hydroxy acid having the formula selected from the group consisting of:



wherein R is hydrogen or a C_1-C_{22} alkyl group.

2. The salt of claim 1 wherein R is hydrogen.

3. The salt of claim 1 wherein R is a C_3-C_{15} alkyl group.

4. The salt of claim 1 wherein the 2-hydroxy acid is selected from the group consisting of glycolic acid, lactic acid, 2-hydroxydecanoic acid, 2-hydroxyoctanoic acid and 2-hydroxylauric acid, and the alkanolamine is selected from the group consisting of monoethanolamine, diethanolamine and triethanolamine.

5. The salt of claim 1 comprising the quaternary salt of glycolic acid with monoethanolamine.

6. The salt of claim 1 comprising the quaternary salt of glycolic acid with diethanolamine.

7. The salt of claim 1 comprising the quaternary salt of glycolic acid with triethanolamine.

8. The salt of claim 1 comprising the quaternary salt of lactic acid with monoethanolamine.

9. The salt of claim 1 comprising the quaternary salt of lactic acid with diethanolamine.

10. The salt of claim 1 comprising the quaternary salt of lactic acid with triethanolamine.

11. The salt of claim 1 comprising the quaternary salt of 2-hydroxydecanoic acid with monoethanolamine.

12. The salt of claim 1 comprising the quaternary salt of 2-hydroxydecanoic acid with diethanolamine.

13. The salt of claim 1 comprising the quaternary salt of 2-hydroxydecanoic acid with triethanolamine.

14. The salt of claim 1 comprising the quaternary salt of 2-hydroxyoctanoic acid with monoethanolamine.

15. The salt of claim 1 comprising the quaternary salt of 2-hydroxyoctanoic acid with diethanolamine.

16. The salt of claim 1 comprising the quaternary salt of 2-hydroxyoctanoic acid with triethanolamine.

17. The salt of claim 1 comprising the quaternary salt of 2-hydroxylauric acid with monoethanolamine.

18. The salt of claim 1 comprising the quaternary salt of 2-hydroxylauric acid with diethanolamine.

19. The salt of claim 1 comprising the quaternary salt of 2-hydroxylauric acid with triethanolamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/04969

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/205, 31/19, 31/20
US CL : 514/554, 557, 558; 554/103, 108, 109, 110; 564/281, 291, 292
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,105,782 A (YU et al.) 08 August 1978, entire document especially column 1, lines 36-44, column 4 and examples 1-5.	1-10
X	US 4,363,815 A (YU et al.) 14 December 1982, entire document, especially column 4, lines 1-10	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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